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PATENT  
Attorney Docket No. 15270J-004766US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Dale B. Schenk et al.

Application No.: 10/777,792

Filed: February 11, 2004

For: PREVENTION AND TREATMENT  
OF AMYLOIDOGENIC DISEASE

Confirmation No. 3041

Examiner: Daniel E. Kolker

Technology Center/Art Unit: 1649

APPELLANT'S BRIEF  
UNDER 37 C.F.R. §41.37

Mail Stop Appeal Brief  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Commissioner:

Further to the Notice of Appeal mailed on March 18, 2009 in the above-referenced application, Appellants submit this Brief on Appeal. A petition to extend the time to submit this Brief from May 18, 2009 to August 18, 2009 is submitted herewith.

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**1. REAL PARTY IN INTEREST**

The real party of interest is Elan Pharma International Limited, assignee of record.

## **2. RELATED APPEALS AND INTERFERENCES**

An Appeal Board has rendered a decision on appeal and a decision on request for rehearing in Appeal Number 2006-3375 for related case, US Application No. 09/723,765. However, the issues in the present case are not analogous to those decided in US Application No. 09/723,765.

Previous appeal briefs have been filed in related cases, US Application Nos. 09/322,289 and 09/724,319. However, in each case, the Examiner reopened prosecution terminating the appeal.

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### **3. STATUS OF CLAIMS**

Claims 1-118 are cancelled. Claims 119-143 are rejected.

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#### **4. STATUS OF AMENDMENTS**

A reply dated February 18, 2009 was filed to the final office action of November 18, 2008. The reply was entered. No amendments were made in the reply.

## **5. SUMMARY OF CLAIMED SUBJECT MATTER**

The application contains two independent claims 119 and 131. Independent claim 119 is directed to a composition comprising an A $\beta$  peptide linked to a carrier which is a toxoid from a pathogenic bacterium to form a conjugate, wherein the A $\beta$  peptide is A $\beta$ 1-7. Such a composition is described at *e.g.*, p. 15, line 4 (A $\beta$ 1-7 fragment), and p. 29, lines 12-13 (toxoid from pathogenic bacteria). The specification also provides a working example showing that such a composition is effective in reducing amyloid burden in a transgenic animal model of Alzheimer's disease (pp. 101-103).

Independent claim 131 is directed to a composition having the same components of claim 119 and an adjuvant (*see* p. 38, line 32-p. 40, line 29).

Claim 133, which depends from claim 131, specifies that the adjuvant is QS-21 (*see* specification at p. 41, line 22).

**6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

1. Whether claims 119, 121-125, and 131 would have been obvious over Selkoe (US 5,262,332) [Selkoe], Wong, PNAS 82,8729-8732 (1985) [Wong] and Penney, US 5,773,007 [Penney].

2. Whether claims 119-125 and 131-132 would have been obvious over Selkoe, Wong, and Penney in further view of Restifo, US 5,733,548 [Restifo].

3. Whether claims 119, 121-125, 131 and 133-138 would have been obvious over Selkoe, Wong and Penney in further view of Hancock, US 5,723,130 [Hancock].

4. Whether claims 119, 121-131 and 133-143 would have been obvious over Selkoe, Wong, Penney and Hancock in further view of Collier, US 5,601,827 [Collier].



## **7. ARGUMENT**

### **7.1 Claims 119, 121-125, and 131 Not Obvious Over Selkoe, Wong and Penney.**

#### **7.1.1 The Examiner's Rationale**

The Examiner's rationale is stated in the penultimate office action of April 3, 2008 at pp. 6-8 and the final office action of November 18, 2008 at pp. 3-7. Selkoe is alleged to teach use of fragments of about 8 or more amino acids of A $\beta$  for immunization to generate antibodies for use in detection (final office action, paragraph bridging pp. 3-4). Wong is alleged to teach a conjugate of A $\beta$ 1-10 to keyhole limpet hemocyanin to generate an antibody to A $\beta$  for use in detection. Wong is acknowledged not to teach A $\beta$  1-7 or linking an A $\beta$  fragment to a pathogenic bacterium (final office action at p. 4, second paragraph). Penney is alleged to teach use of carriers such as keyhole limpet hemocyanin and toxoids from pathogenic bacteria (final office action at p. 4, 3rd paragraph). The Examiner alleges that it would have been obvious to combine Selkoe's teaching of about 8 amino acids with Wong's teaching of A $\beta$ 1-10 to arrive at A $\beta$  1-7 for the benefit of making more antibodies to A $\beta$  for use in diagnosis (final office action at p. 4, last paragraph) and because a shorter peptide would be cheaper to make (final office action at p. 6, first and second paragraphs). The Examiner further alleges that it would have been obvious to substitute KLH with CRM197 as Penney teaches that a heterologous peptide can be used to increase antigenicity (final office action at p. 5, first sentence).

#### **7.1.2 The Cited Art**

Wong discusses KLH as a carrier for an A $\beta$  fragment for immunization of laboratory animals as a means to generate antibodies (*see* paragraph bridging pp. 8729-30). Wong provides no indication that immunization with A $\beta$  has any therapeutic application in humans.

Penney teaches that KLH is a preferred carrier for animal use (*see e.g.*, col. 5, lines 2-4). By contrast, Penney teaches that toxoids from pathogenic bacteria are suitable and commonly used for human use (*see, e.g.*, col. 2, lines 5-8; col. 5, lines 4-12).

Selkoe discusses using antibodies to A $\beta$  for diagnosis of Alzheimer's disease (paragraph bridging cols. 4 and 5). Antibodies are produced by conventional immunization of a laboratory animal with either amyloid containing A $\beta$  or a synthetic peptide (cols. 17-18). Although Selkoe asserts that some fragments of about 8 or more amino acids from A $\beta$  are capable of producing antibodies (col. 4, lines 18-24), he also reports that antibodies raised against amyloid deposits showed stronger staining than an antibody to a synthetic peptide containing residues 1-29 of A $\beta$  (*see* column 21, lines 13-26).

#### 7.1.3 The Cited Art Distinguished

Appellants respectfully submits that a *prima facie* case of obviousness has not been established because there was no reason to replace Wong's use of KLH in animals with a toxoid from a pathogenic bacteria and insufficient reason to replace Wong's 1-10 fragment with an A $\beta$  1-7 fragment.

Although motivation is not applied as a rigid formula denying recourse to common sense, it can still be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *KSR International Co. v. Teleflex Inc.*, 550 US 398, 418, 82 USPQ2d 1385, 1396 (U.S. 2007). Furthermore, a factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. *Id.* at 421. 82 USPQ2d 1385, 1397 (U.S. 2007).

It would not have been obvious to replace Wong's use of KLH in animals with a toxoid from a pathogenic bacteria because Penney teaches that Wong was already using the preferred carrier for animal use (*see, e.g.*, col. 5, lines 2-4). Wong provides no indication of a potential human use that would have suggested any compensating benefit for foregoing the preferred carrier for animal use in favor of a toxoid from a pathogenic bacteria, taught by Penney as being suitable for human use. Without any indication of a human use by Wong, the purported switch from KLH to a toxoid from a pathogenic bacterium appears not to reflect the common sense approach of the artisan but instead an impermissible hindsight reconstruction of the claimed invention.

Furthermore, the combination of Wong and Selkoe, neither of which contemplated administration of an immunogen to humans, did not provide a reason to select an antibody binding to an epitope within residues 1-7 of A $\beta$  or to make the claim compositions to elicit such an antibody. As shown in Table 16 of the present application (p. 99), antibodies binding to an epitope within residues 1-7 of A $\beta$  are particularly advantageous relative to antibodies with other epitope specificities in clearing A $\beta$  deposits in a transgenic mouse model and in an *ex vivo* assay. The purported selection of Wong is not based on recognition of this or other advantage of such an antibody, but an impermissible hindsight reconstruction resulting from selective reliance on only part of the art.

Although Wong discusses an antibody binding within residues 1-10 of A $\beta$ , he does not provide any reason to think that this antibody is any better for diagnosis than any other antibody to A $\beta$ . Wong's selection of an antibody to the first ten residues of A $\beta$  can be rationalized from the perspective that the full sequence of A $\beta$  was not available at the time (*see* Fig. 1 of Wong providing only the first 28 residues of a peptide), and the first ten residues were most likely to be free from error due to amino acids being identified starting with the N-terminus. Consistent with this view residue 11 of the Alzheimer's A $\beta$  sequence shown by Wong is wrong (Gln instead of Glu) (*see* Fig. 1, upper sequence compared with SEQ ID NO:42 of the present application). In the passage of time between Wong and the effective filing date of the present application, the full-and correct sequence of A $\beta$  became well-known and many antibodies were generated to various parts of the molecule (*see, e.g.,* Iwatsubo, *Neuron*, 13:45-53 (1994) discussing C-terminal antibodies and WO 90/12871, reporting stronger staining with antibodies to a 17-24 epitope. Viewing the art in its totality, there was no reason to select Wong's antibody rather than any of the numerous other antibodies to A $\beta$  subsequently described in the art for diagnosis.

Selkoe casts additional doubt on the proposition that Wong's antibody would have been selected based on advantages in diagnosis. Selkoe reports that antibodies raised against amyloid deposits showed stronger staining than an antibody to a synthetic peptide (*see* column 21, lines 13-26). Such teaching would have discouraged the use of small synthetic fragments of A $\beta$  for generating antibodies for purposes of diagnosis. Thus, if diagnosis by detecting A $\beta$  were

one's goal, and one were to have relied only on Wong's and Selkoe's teaching, one would presumably have selected an antibody raised against A $\beta$  deposits rather than Wong's antibody to a synthetic peptide.

Selkoe also does not suggest replacing Wong's antibody with an antibody binding to an epitope within residues 1-7 of A $\beta$ . A fair reading of Selkoe's comment that some fragments of about 8 or more residues can be used for generating antibodies is that a fragment of 8 residues is about the minimum size and that if a smaller fragment is used there is at least a risk of failure. There is no apparent reason in either Wong or Selkoe that the artisan would have felt compelled to test the limits of fragment size and risk possible failure in generating an antibody rather than following the protocol of Wong (who used an A $\beta$ 1-10 fragment) or Selkoe who used an A $\beta$ 1-28 fragment. Common sense suggests such possible failure would have appeared to involve an unnecessary risk of more concern than any minor cost saving from synthesizing a slightly shorter peptide, which risk the artisan could have avoided by using a longer fragment as in Wong. Furthermore, even if the artisan had the fortitude to test the boundaries of feasibility of fragment size, there would have been no reason for him to select an A $\beta$ 1-7 fragment, rather than an A $\beta$  2-8, or A $\beta$ 3-9 fragment or indeed any other seven amino acid fragment from A $\beta$ .

Patentability is further evidenced by two unexpected results of the claimed conjugate vis-a-vis the cited art. The claimed conjugate is an unexpectedly superior agent for human therapeutic administration than the A $\beta$ 1-10-KLH-conjugate discussed by Wong. The superiority arises in part because toxoid from a pathogenic bacterium is more suitable for human use whereas KLH is a preferred carrier for animal use (*see* Penney, col. 2, lines 5-8; and col. 5, lines 4-12). Although the advantage of toxoids from pathogenic bacteria from human use had already been reported by Penney, the advantage of the claimed conjugates is unexpected because the cited art did not teach that the claimed conjugates had any use in humans. Without the insight provided by the present application that the claimed conjugates have a therapeutic use in humans, the claimed conjugates would have appeared disadvantageous relative to those of the art because the art was already using the preferred carrier for animal use. The advantageous property of the claimed conjugates for use in humans vis-a-vis the cited art can only be viewed as unexpected.

The claimed conjugates are also unexpectedly advantageous for therapeutic use relative to Wong's A $\beta$ 1-10 fragment because the claimed use of A $\beta$ 1-7 preserves three epitopes predominantly responsible for plaque clearing effects, but reduces the likelihood of T-cell mediated side effects. Table 16 in the present application shows three epitope specificities that are particularly effective in clearing amyloid deposits: A $\beta$ 1-5, 3-6 and 3-7. The A $\beta$ 1-7 fragment includes each of these three epitopes. Furthermore, Rammensee, *Curr. Opin. Immunol.*, 1995, 7:85-96 reports that T-cell epitopes are normally at least 9 amino acids long. The claimed A $\beta$ 1-7 fragment is smaller than this size, whereas the A $\beta$ 1-10 fragment of Wong is longer. Accordingly, the A $\beta$ 1-7 fragment is likely to be even less susceptible to generating T-cells than Wong's fragment. Post-filing data have shown that T-cell mediated effects can give rise to side effects in a small proportion of patients (Hock, *Neuron*, 2003, 38: 543-554; and, WO 04/069182 at paragraph 0034. Accordingly, a reduction in such side effects is a significant unexpected advantage.

The Examiner cites MPEP § 2143 for the proposition that choosing between a finite number of carriers would have been obvious (final office action at p. 5, last paragraph). However, the present facts and circumstances are distinguishable from the case law underlying MPEP § 2143. Both Pfizer (*Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007)) and Alza (*Alza Corp. v. Mylan Laboratories, Inc.*, 461 F.3d 1286, 80 USPQ2d 1001 (Fed. Cir. 2006)) involved selection of auxiliary substances for known therapeutic agents. By contrast, A $\beta$ 1-7 was not known to have any therapeutic properties. Thus, the advantage of the claimed conjugates vis-a-vis the art for human administration can only be viewed as unexpected. Furthermore, as discussed above, the use of A $\beta$ 1-7 confers additional advantages beyond the selection of carriers.

The Examiner also cited MPEP § 2123(I) for the proposition that even non-preferred embodiments are to be considered in making determinations of obviousness (final office action at p. 5, last paragraph). Although MPEP § 2123(I) provides that non-preferred embodiments constitute prior art, it does not say that the characterization of one element of a claim as non-preferred is determinative that the claim as a whole is obvious. The cases cited in MPEP § 2123(I) involve unrelated facts and circumstances to the present. Two of the cases

(*Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 75 USPQ2d 1213 (Fed. Cir. 2005); and *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 47 USPQ2d 1516 (Fed. Cir. 1998)) involved anticipation, the issue being whether a single reference disclosing an embodiment of an invention characterized as non-preferred still anticipated. The third case (*Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)) involved obviousness based on a single reference. The invention in *Merck* was a combination of a first component and a second component, both of which were known drugs. The prior art reference disclosed that a genus of 10 drugs (comprising the first component) could be combined with another genus of 120 drugs (comprising the second component) for the identical purpose as claimed. Neither the first component, nor the second component, however, was highlighted as a preferred embodiment in the prior art reference. Against this background, the court stated "all disclosures of the prior art, including unpreferred embodiments, must be considered." *Id.* at 807.

*Merck* is clearly distinguishable on its facts. *Merck* involved the combination of two drugs from two lists of drugs, the combination having the same use as the individual drugs. Neither of the drugs was highlighted as being either favored or disfavored in the respective lists. Here, the case of alleged obviousness is based on two references. One of the references (Wong) discusses a 1-10 A $\beta$  fragment linked to KLH for use as research reagent in animals. The other reference (Penney) teaches that KLH is the preferred carrier for research use in animals and that toxoids from pathogenic bacteria are preferred for therapeutic use in humans. The case of obviousness is not simply a combination of two similar substances from different lists but the replacement of what would have appeared to have been a more preferred substance with a less preferred substance as a result of which unexpectedly, the combination confers an improved suitability for human use. The issue is not whether Penney's teaching constitutes prior art, but whether the claimed conjugates would have been obvious in light of such teaching. In appellant's submission, this teaching only serves to reinforce the unexpected result discussed above; namely that the claimed conjugates have an unexpectedly advantageous property relative to the art conjugates of improved suitability for human administration. This property could not

have been expected without knowledge that the claimed conjugates had a therapeutic role in humans.

For these reasons, it is respectfully submitted that the rejection should be reversed.

7.2 Claims 119-125 and 131-132 Not Obvious Over Selkoe, Wong, and Penney in further view of Restifo

Selkoe, Wong, and Penney are applied as in section 7.1 above. Restifo is alleged to teach using multiple copies of a peptide as an immunogen (final office action at p. 7, 5<sup>th</sup> and 6<sup>th</sup> paragraphs). Claims 119-125 and 131-132 would have been nonobvious for at least the same reasons as discussed in section 7.1 above.

7.3 Claims 119, 121-125, 131 and 133-138 Not Obvious over Selkoe, Wong and Penney in further view of Hancock

Selkoe, Wong and Penney are applied as in section 7.1. Hancock is alleged to teach use of QS-21 as an adjuvant. The Examiner alleges it would have been obvious to use QS-21 as an adjuvant in view of Hancock alleged teaching that it is particularly effective in eliciting antibodies (penultimate office action at p. 9, second paragraph, final office action at p. 8, 3<sup>rd</sup> paragraph).

The distinctions discussed in section 7.1 are equally applicable here. In addition, Hancock would not have motivated replacement of Freund's adjuvant used by Wong in favor of QS-21.

Hancock discusses QS-21 in the context of a vaccine against a virus--RSV--intended for human administration. RSV is not a self-antigen such as A $\beta$ . QS-21 is indicated to enhance stimulation of antibodies relative to alum (an adjuvant commonly used in humans) or relative to no adjuvant (*see e.g.*, col. 3, lines 3-7). However, QS-21 is not indicated to improve or even be equally effective for stimulation of antibodies relative to Freund's adjuvant, the adjuvant used by Wong. Freund's adjuvant is the most commonly used adjuvant for animal administration (Harlow & Lane, *Antibodies: A Laboratory Manual* (CSHL 1988)) at p. 98, and

is characterized as a "potent immunostimulant" but restricted to animal use (Penney paragraph bridging cols. 2-3). Also, the stimulation reported by Hancock is only in the context of antibodies against RSV and it would have been unclear whether QS-21 would have been advantageous even relative to alum in other contexts. Absent any recognition of potential administration of A $\beta$  to humans by Wong, a report that one adjuvant suitable for human use was better than another in the context of an RSV vaccine would not have been seen as relevant to Wong's goal of generating antibodies to A $\beta$  in a laboratory animal.

The Examiner characterizes this position as an argument for lack of expectation of success, which the Examiner dismisses as merely attorney argument (final office action at p. 8, last paragraph). In fact, however, the Examiner is addressing an argument that was never made. Appellant's position was directed to the lack of motivation or other reason to replace Freund's adjuvant with QS-21, not the expectation of success were such a replacement to have occurred.

The purported replacement of Freund's adjuvant with QS-21 is in some ways analogous to the purported replacement of KLH with a toxoid from a pathogenic bacteria. The replacement of Freund's adjuvant with QS-21 confers an unexpected benefit for use in humans but at a cost of foregoing the most commonly used adjuvant in animals. The benefit in humans is unexpected because A $\beta$ 1-7 was not known to have any therapeutic use in humans, as discussed previously.

Although MPEP § 2123(I) provides that non-preferred embodiments constitute prior art, it does not say that the characterization of one element of a claim as non-preferred is determinative that the claim as a whole is obvious. Furthermore, with respect to MPEP § 2144.06, Freund's adjuvant and QS-21 are not recognized as equivalents in the art of record. Freund's adjuvant is a potent adjuvant and the most commonly used adjuvant used in animals but restricted to use in animals (Penney paragraph bridging cols. 2-3). QS-21 is reported to be suitable for use in humans but of unknown relative potency relative to Freund's adjuvant for use in animals.

Because the present claims confer an advantage not shared by the art (*i.e.*, suitability for use in humans), which could not have been appreciated absent recognition of a



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therapeutic role for A $\beta$ 1-7, and for the reasons discussed in the previous response, it is submitted that the rejection should be withdrawn.

7.4. Claims 119, 121-131 and 133-143 Not Obvious Over Selkoe, Wong, Penney and Hancock in further view of Collier.

Selkoe, Wong, Penney, Hancock are applied as above. Collier is alleged to teach fusion of an immunogen to CRM197 (final office action at p. 9, fourth paragraph). This combination of references is distinguished for at least the reasons provided in 7.3 above.

For these reasons, it is respectfully submitted that the rejection should be reversed.

Respectfully submitted,



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## **8. CLAIMS APPENDIX**

119. A composition comprising an A $\beta$  peptide linked to a carrier which is a toxoid from a pathogenic bacterium to form a conjugate, wherein the A $\beta$  peptide is A $\beta$ 1-7.
120. The composition of claim 119, wherein the conjugate comprises a plurality of additional copies of A $\beta$ 1-7.
121. The composition of claim 119, which comprises at least 10  $\mu$ g of A $\beta$ 1-7.
122. The composition of claim 119, which comprises at least 20  $\mu$ g of A $\beta$ 1-7.
123. The composition of claim 119, which comprises at least 50  $\mu$ g of A $\beta$ 1-7.
124. The composition of claim 119, which comprises at least 100  $\mu$ g of A $\beta$ 1-7.
125. The composition of claim 119, wherein the carrier is a diphtheria toxoid and A $\beta$ 1-7 is linked to the diphtheria toxoid by chemical crosslinking.
126. The composition of claim 125, wherein the amino terminus of A $\beta$ 1-7 is linked to the diphtheria toxoid.
127. The composition of claim 125, wherein the carboxyl terminus of A $\beta$ 1-7 is linked to the diphtheria toxoid.
128. The composition of claim 119, wherein the conjugate is expressed as a fusion protein.
129. The composition of claim 128, wherein the toxoid is a diphtheria toxoid and the amino terminus of A $\beta$ 1-7 is linked to the diphtheria toxoid.
130. The composition of claim 128, wherein the toxoid is a diphtheria toxoid and the carboxyl terminus of A $\beta$ 1-7 is linked to the diphtheria toxoid.

131. A composition comprising (a) an A $\beta$  peptide linked to a carrier which is a toxoid from a pathogenic bacterium to form a conjugate, wherein the A $\beta$  peptide is A $\beta$ 1-7 and (b) an adjuvant.

132. The composition of claim 131, wherein the conjugate comprises a plurality of additional copies of A $\beta$ 1-7.

133. The composition of claim 131, wherein the adjuvant comprises QS-21.

134. The composition of claim 133, which comprises at least 10  $\mu$ g of A $\beta$ 1-7.

135. The composition of claim 133, which comprises at least 20  $\mu$ g of A $\beta$ 1-7.

136. The composition of claim 133, which comprises at least 50  $\mu$ g of A $\beta$ 1-7.

137. The composition of claim 133, which comprises at least 100  $\mu$ g of A $\beta$ 1-7.

138. The composition of claim 133, wherein the toxoid is diphtheria toxoid and A $\beta$ 1-7 is linked to the diphtheria toxoid by chemical crosslinking.

139. The composition of claim 138, wherein the amino terminus of A $\beta$ 1-7 is linked to the diphtheria toxoid.

140. The composition of claim 138, wherein the carboxyl terminus of A $\beta$ 1-7 is linked to the diphtheria toxoid.

141. The composition of claim 133, wherein the conjugate is expressed as a fusion protein.

142. The composition of claim 141, wherein the toxoid is diphtheria toxoid and the amino terminus of A $\beta$ 1-7 is linked to the diphtheria toxoid.

143. The composition of claim 141, wherein the toxoid is diphtheria toxoid and the carboxyl terminus of A $\beta$ 1-7 is linked to diphtheria toxoid.

**9. EVIDENCE APPENDIX**

Iwatsubo, *Neuron*, 13:45-53 (1994), cite no. 192 in the IDS filed February 6, 2007, entered May, 8, 2007.

WO 90/12871 cite no. 85 in the IDS filed February 6, 2007, entered May, 8, 2007.

Rammensee, *Curr. Opin. Immunol.*, 1995, 7:85-96, cited as cite no. 928 by the supplemental IDS filed August 29, 2008, entered November 18, 2008.

Hock, *Neuron*, 2003, 38: 543-554, cite no. 534 in the supplemental IDS filed February 6, 2007, entered May, 8, 2007.

WO 04/069182 cite no. 918 in the supplemental IDS filed August 29, 2008, entered, November 18, 2008.

Harlow & Lane, *Antibodies: A Laboratory Manual* (CSHL 1988)) at p. 98, cite no. 931 in the supplemental IDS filed August 29, 2008, entered November 18, 2008.

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**10. RELATED PROCEEDINGS APPENDIX**

Copies of the decision on appeal and the decision on request for rehearing in  
Appeal Number 2006-3375 for related case US Application No. 09/723,765 are attached hereto.